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FILE LAST UPDATED: 30 Nov 2008 (20081130/ED)

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=> s 106941-25-7 and (lymph#### or liver or hematologic## or kidney or nephr#####
or or hepatic)
REGISTRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

L2 794 L1

MISSING TERM 'OR OR'
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The search profile that was entered contains a logical
operator followed immediately by another operator.

=> s L2 and (hiv or immunodeficiency or hbv or hepatitis)
81787 HIV
108 HIVS
81808 HIV
(HIV OR HIVS)

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         83097 IMMUNODEFICIENCY
           848 IMMUNODEFICIENCIES
         83397 IMMUNODEFICIENCY
                 (IMMUNODEFICIENCY OR IMMUNODEFICIENCIES)
         13192 HBV
            83 HBVS
         13211 HBV
                 (HBV OR HBVS)
         70822 HEPATITIS
             1 HEPATITISES
         70822 HEPATITIS
                 (HEPATITIS OR HEPATITISES)
L3         472 L2 AND (HIV OR IMMUNODEFICIENCY OR HBV OR HEPATITIS)

=> s L3 and (administ##### or measur### or determin### or quantif#####)
        291157 ADMINIST#####
       2141839 MEASUR###
        206482 DETERMIN###
        745940 DET
         47599 DETS
        789559 DET
                 (DET OR DETS)
       2236687 DETD
        371230 DETG
       1609736 DETN
        136960 DETNS
       1690562 DETN
                 (DETN OR DETNS)
       4395243 DETERMIN###
                 (DETERMIN### OR DET OR DETD OR DETG OR DETN)
        125920 QUANTIF#####
L4         121 L3 AND (ADMINIST##### OR MEASUR### OR DETERMIN### OR QUANTIF####
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=> s L4 and (pharmacokinetic# or bioavailab##### or distribution)
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         70286 BIOAVAILAB#####
       1194690 DISTRIBUTION
        221574 DISTRIBUTIONS
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L5          18 L4 AND (PHARMACOKINETIC# OR BIOAVAILAB##### OR DISTRIBUTION)

=> s L5 and py<2004
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L6          10 L5 AND PY<2004

=> d L6 ibib abs 1-10

L6   ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2002:695941  CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER:          137:232453
TITLE:                    Preparation of substituted benzophenones as inhibitors
                          of reverse transcriptase
INVENTOR(S):              Chan, Joseph Howing
PATENT ASSIGNEE(S):       Smithkline Beecham Corporation, USA
SOURCE:                   PCT Int. Appl., 163 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
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PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 2002070470	A2	20020912	WO 2002-US6037	20020228	<--
WO 2002070470	A3	20030306			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2439820	A1	20020912	CA 2002-2439820	20020228	<--
AU 2002254056	A1	20020919	AU 2002-254056	20020228	<--
AU 2002254056	B2	20050929			
EP 1363877	A2	20031126	EP 2002-723265	20020228	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
HU 2003003326	A2	20040128	HU 2003-3326	20020228	
BR 2002007752	A	20040323	BR 2002-7752	20020228	
CN 1494528	A	20040505	CN 2002-805882	20020228	
NZ 527864	A	20040528	NZ 2002-527864	20020228	
JP 2004525914	T	20040826	JP 2002-569791	20020228	
IN 2003KN01052	A	20050708	IN 2003-KN1052	20030819	
ZA 2003006549	A	20041122	ZA 2003-6549	20030821	
NO 2003003857	A	20031027	NO 2003-3857	20030901	<--
MX 2003PA07883	A	20031204	MX 2003-PA7883	20030902	<--
US 20040122064	A1	20040624	US 2004-469104	20040205	
US 6995283	B2	20060207			
US 20060009651	A1	20060112	US 2005-223634	20050909	
PRIORITY APPLN. INFO.:			US 2001-272953P	P 20010302	
			WO 2002-US6037	W 20020228	
			US 2004-469104	A3 20040205	

OTHER SOURCE(S): MARPAT 137:232453
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1 = ≥1 substituent chosen from halo, CF3, alkyl, aminoalkyl, alkoxy, CN, NO2, NH2, thioalkoxy, etc.; R2 = H, halo, alkyl, NO2, NH2, alkylamino, CF3, alkoxy; R3 = OH, halo, CF3, NO2, alkyl; R4 = sulfonamido, sulfonylimino, etc.;] were prepared For instance, 3,5-dichlorobromobenzene was metalated (MTBE, n-BuLi, -50°) and acylated with the N,2-dimethoxy-N-methyl-5-chlorobenzamide and the resulting benzophenone converted to II. II was converted to III in 5 steps. Polymorphic forms of sodium, choline, calcium, magnesium, ethanolamine and triethylamine salts of III were prepared and characterized. Oral bioavailability and solubility parameters were determined for III and polymorphic salt forms thereof. Compds. of the present invention have anti-HIV activity and deliver compds. that have anti- HIV activity in the range IC50 = 1-1000 nM against wild type and mutant viruses.

L6 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:684966 CAPLUS <<LOGINID::20081202>>

DOCUMENT NUMBER: 138:297033
TITLE: Pharmacokinetic and antiretroviral activity in mice of oral [P1,P2-bis[2-(adenin-9-yl)ethoxymethyl]phosphonate], a prodrug of 9-(2-phosphonylmethoxyethyl)adenine
AUTHOR(S): Rossi, Luigia; Dominici, Sabrina; Serafini, Sonja; Casabianca, Anna; Cerasi, Aurora; Chiarantini, Laura; Celeste, Angela Gabriela; Cappellacci, Loredana; Franchetti, Palmarisa; Grifantini, Mario; Magnani, Mauro
CORPORATE SOURCE: Institute of Biochemistry 'G. Fornaini', University of Urbino, Urbino, 61029, Italy
SOURCE: Journal of Antimicrobial Chemotherapy (2002), 50(3), 365-374
CODEN: JACHDX; ISSN: 0305-7453
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 9-(2-Phosphonylmethoxyethyl)adenine (PMEA) is an antiviral drug with activity against herpes viruses, Epstein-Barr virus, and retroviruses, including the human immunodeficiency virus. Unfortunately, oral PMEA administration, as required for long-term therapy, is hindered by its low bioavailability. In the present study, the synthesis, oral bioavailability and antiretroviral activity of a new prodrug of PMEA, consisting of 2 mols. of PMEA bound together by a P-O-P bond (Bis-PMEA), are reported. Pharmacokinetic expts. in mice showed that the oral bioavailabilities of PMEA following oral gavage of Bis-PMEA or PMEA (at a dose equivalent to 28 mg of PMEA/kg) were 50.8 and 13.5%, resp. These results correlate with the antiviral efficacy of Bis-PMEA administered orally at a dose equivalent to 50 mg/kg of PMEA in C57 BL/6 mice infected with the retroviral complex LP-BM5. Oral treatment with Bis-PMEA proved to be more effective than oral treatment with PMEA given at equimolar doses. Moreover, oral Bis-PMEA was more effective than i.p. PMEA (50 mg/kg) in reducing lymphoadenopathy, hypergammaglobulinemia and lymph node proviral DNA content, overall in the 1st weeks post virus inoculation. Bis-PMEA thus appears to be an efficient oral prodrug of PMEA without significant toxicity, at least in this mouse model.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:714117 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 136:48011
TITLE: Antiviral efficacy and pharmacokinetics of oral adefovir dipivoxil in chronically woodchuck hepatitis virus-infected woodchucks
AUTHOR(S): Cullen, John M.; Li, Daniel H.; Brown, Cynthia; Eisenberg, Eugene J.; Cundy, Kenneth C.; Wolfe, Julie; Toole, Jay; Gibbs, Craig
CORPORATE SOURCE: North Carolina State University College of Veterinary Medicine, Raleigh, NC, 27606, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2001), 45(10), 2740-2745
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antiviral efficacy of orally administered adefovir dipivoxil was evaluated in an 18-wk study (12 wk of treatment and 6 wk of recovery) conducted with woodchucks chronically infected with woodchuck hepatitis virus (WHV). Adefovir dipivoxil is a prodrug of

adefovir designed to enhance its oral bioavailability. Following administration of 15 mg of adefovir dipivoxil per kg of body weight in 4 WHV-infected animals, the mean maximum concentration of adefovir in blood serum was 0.462 μg/mL, with an elimination half-life of 10.2 h, and the oral bioavailability of adefovir was estimated to be 22.9% (±11.2%). To study antiviral efficacy, the animals were divided into 3 groups. There were 6 animals each in a high-dose group (15 mg/kg/day) and a low-dose group (5 mg/kg/day). A vehicle control group consisted of 5 animals because WHV DNA was detectable only by PCR at the time of the study in one of the original 6 animals. Efficacy was evaluated by determining the levels of WHV DNA in serum. The geometric mean WHV DNA level for the high-dose group diminished by >40-fold (>1.6 log10) after 2 wk of treatment and >300-fold (>2.5 log10) at 12 wk. There was a >10-fold reduction in 5 of 6 low-dose animals by 2 wk, but levels were unchanged in 1 animal. By 12 wk of treatment there was a >45-fold (>1.6 log10) reduction of WHV DNA levels, and serum WHV DNA levels were below the limit of quantification in 3 of 6 animals. Viral DNA levels returned to pretreatment levels during the 6-wk recovery period. There were no clin. significant changes in body weight, hematol., or serum chemical values, including bicarbonate or lactate, in any of the treated animals. No histol. evidence of liver injury was apparent in the biopsies. Under the conditions of this study, adefovir dipivoxil was an effective antihepadnaviral agent.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:662859 CAPLUS <<LOGINID::20081202>>

DOCUMENT NUMBER: 134:33070

TITLE: Novel hepatotrophic prodrugs of the antiviral nucleoside 9-(2-phosphonylmethoxyethyl)adenine with improved pharmacokinetics and antiviral activity

AUTHOR(S): Biessen, E. A. L.; Valentijn, A. R. P. M.; de Vrueh, R. L. A.; van de Bilt, E.; Sliedregt, L. A. J. M.; Prince, P.; Bijsterbosch, M. K.; van Boom, J. H.; van der Marel, G. A.; Abrahms, P. J.; van Berkel, T. J. C.

CORPORATE SOURCE: Division of Biopharmaceutics, LACDR, LIC Leiden University, Leiden, Neth.

SOURCE: FASEB Journal (2000), 14(12), 1784-1792
CODEN: FAJOEC; ISSN: 0892-6638

PUBLISHER: Federation of American Societies for Experimental Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The device of new hepatotrophic pro-drugs of the antiviral nucleoside 9-(2-phosphonylmethoxyethyl)adenine (PMEA) with specificity for the asialoglycoprotein receptor on parenchymal liver cells is described. PMEA was conjugated to bi-and trivalent cluster glycosides (K(GN)2 and K2(GN)3, resp.) with nanomolar affinity for the asialoglycoprotein receptor. The liver uptake of the PMEA prodrugs was more than 10-fold higher than that of the parent drug (52±6% and 62±3% vs. 4.8±0.7% of the injected dose for PMEA) and could be attributed for 90% to parenchymal cells. Accumulation of the PMEA prodrugs in extrahepatic tissue (e.g., kidney, skin) was substantially reduced. The ratio of parenchymal liver cell-to-kidney uptake - a measure of the prodrugs therapeutic window - was increased from 0.058 ± 0.01 for PMEA to 1.86 ± 0.57 for K(GN)2-PMEA and even 2.69 ± 0.24 for K2(GN)3-PMEA. Apparently both glycosides have a similar capacity to redirect (antiviral) drugs to the liver. After cellular uptake, both PMEA prodrugs were converted into the

parent drug, PMEA, during acidification of the lysosomal milieu (t1/2≈100 min), and the released PMEA was rapidly translocated into the cytosol. The antiviral activity of the prodrugs in vitro was dramatically enhanced as compared to the parent drug (5- and 52-fold for K(GN)2-PMEA and K2(GN)3-PMEA, resp.). Given the 15-fold enhanced liver uptake of the prodrugs, we anticipate that the potency in vivo will be similarly increased. We conclude that PMEA prodrugs have been developed with greatly improved pharmacokinetics and therapeutic activity against viral infections that implicate the liver parenchyma (e.g., HBV). In addition, the significance of the above prodrug concept also extends to drugs that intervene in other liver disorders such as cholestasis and dyslipidemia.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1998:120883 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 128:225760
ORIGINAL REFERENCE NO.: 128:44565a,44568a
TITLE: Efficacy of the acyclic nucleoside phosphonates (S)-9-(3-fluoro-2-phosphonylmethoxypropyl)adenine (FPMPA) and 9-(2-phosphonylmethoxyethyl)adenine (PMEA) against feline immunodeficiency virus
AUTHOR(S): Hartmann, Katrin; Kuffer, Manuela; Balzarini, Jan; Naesens, Lieve; Goldberg, Michel; Erfle, Volker; Goebel, Frank-Detlef; De Clercq, Erik; Jindrich, Jindrich; Holy, Antonin; Bischofberger, Norbert; Kraft, Wilfried
CORPORATE SOURCE: I. Medizinische Tierklinik, Ludwig-Maximilians-Universitat Munchen, Munich, D-80539, Germany
SOURCE: Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology (1998), 17(2), 120-128
CODEN: JDSRET; ISSN: 1077-9450
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The acyclic nucleoside phosphonates (S)-9-(3-fluoro-2-phosphonylmethoxypropyl)adenine (FPMPA) and 9-(2-phosphonylmethoxyethyl)adenine (PMEA) were evaluated for their efficacy and side effects in a double-blind placebo-controlled trial using naturally occurring feline immunodeficiency virus (FIV)-infected cats. This natural retrovirus animal model is considered highly relevant for the pathogenesis and chemotherapy of HIV in humans. Both PMEA and FPMPA proved effective in ameliorating the clin. symptoms of FIV-infected cats, as measured by several clin. parameters including the incidence and severity of stomatitis, Karnofsky's score, immunol. parameters such as relative and absolute CD4+ lymphocyte counts, and virol. parameters including proviral DNA levels in peripheral blood mononuclear cells (PBMC) of drug-treated animals. In contrast with PMEA, FPMPA showed no hematol. side effects at a dose that was 2.5-fold higher than PMEA.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1997:758718 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 128:162583
ORIGINAL REFERENCE NO.: 128:31855a,31858a
TITLE: Anti-HIV activity of adefovir (PMEA) and PMPA in combination with antiretroviral compounds: in

vitro analyses
AUTHOR(S): Mulato, A. S.; Cherrington, J. M.
CORPORATE SOURCE: Gilead Sciences, Lakeside Drive, Foster City, CA 94404, 333, USA
SOURCE: Antiviral Research (1997), 36(2), 91-97
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Adefovir (PMEA, 9-(2-phosphonomethoxyethyl)adenine), an acyclic nucleoside phosphonate analog is active against retroviruses, hepadnaviruses and herpesviruses. Adefovir dipivoxil, an orally bioavailable prodrug of adefovir is currently in phase III clin. trials for the treatment of HIV and phase II clin. trials for the treatment of HBV infections. PMPA (9-(2-phosphonomethoxypropyl)adenine) is a related acyclic nucleoside phosphonate analog that has demonstrated potent anti-SIV activity in rhesus macaques and recently has shown marked anti-HIV activity in a phase I clin. study. Since the standard of care for AIDS patients has become combination therapy, the effects of other antiretroviral compds. (d4T, ddC, AZT, ddI, 3TC, nelfinavir, ritonavir, indinavir, and saquinavir) on the anti-HIV activity of adefovir and PMPA were investigated in vitro. Adefovir and PMPA both demonstrated strong synergistic anti-HIV activity in combination with AZT. Adefovir demonstrated minor to moderate synergistic inhibition of HIV replication in combination with PMPA, d4T, ddC, nelfinavir, ritonavir, and saquinavir. PMPA demonstrated minor synergistic inhibition of HIV replication in combination with ddI and nelfinavir (and adefovir). All other combinations showed additive inhibition of HIV replication in vitro. Importantly, no antagonistic interactions were measured for any of the adefovir or PMPA combinations.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:566429 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 125:265058
ORIGINAL REFERENCE NO.: 125:49161a,49164a
TITLE: In vitro selection and molecular characterization of human immunodeficiency virus type 1 with reduced sensitivity to 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA)
AUTHOR(S): Foli, Andrea; Sogocio, Kristina M.; Anderson, Barry; Kavlick, Mark; Saville, M. Wayne; Wainberg, Mark A.; Gu, Zhengxian; Cherrington, Julie M.; Mitsuya, Hiroaki; et al.
CORPORATE SOURCE: Medicine Branch, National Cancer Institute, Bethesda, MD, 20892-1906, USA
SOURCE: Antiviral Research (1996), 32(2), 91-98
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 9-[2-(Phosphonomethoxy)ethyl]adenine (PMEA) is an acyclic nucleotide with potent in vitro activity against human immunodeficiency virus type 1 (HIV-1). The present study was undertaken to det. whether HIV-1 resistance to PMEA could be generated by in vitro selection and if so, to determine which mutations in reverse transcriptase (RT) were responsible. HIV-1LAI was serially passaged for 10 mo in the presence of increasing concns. of PMEA up to a maximum of 40 μM. After 40 passages, the 50% inhibitory concentration (IC50) of

PMEA had increased almost 7-fold from 4.45 to 30.5 μM. Some cross-resistance to 2',3'-dideoxycytidine (ddC, zalcitabine), 2',3'-dideoxyinosine (ddI, didanosine), and 3'-thiacytidine (3TC, lamivudine) was also observed, but no cross-reactive resistance to 3'-azido-3'-thymidine (AZT, zidovudine). Sequencing of the RT encoding region of each of eight pol clones from resistant isolates revealed a Lys-65→Arg (K65R) substitution. HIV with the K65R mutation inserted by site-directed mutagenesis also had decreased sensitivity to PMEA in H9 cells and a similar cross-resistance profile. Thus, HIV can develop decreased sensitivity to PMEA after long-term in vitro exposure and this change is associated with a K65R substitution. Addnl. studies will be needed to determine whether a similar mutation in HIV RT develops in patients receiving PMEA or its orally bioavailable prodrug adefovir dipivoxil (bis-POM PMEA).

L6 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1996:19694 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 124:134856
ORIGINAL REFERENCE NO.: 124:24755a,24758a
TITLE: Antiretroviral activity and pharmacokinetics in mice of oral bis(pivaloyloxymethyl)-9-(2-phosphonylmethoxyethyl)adenine, the bis(pivaloyloxymethyl) ester prodrug of 9-(2-phosphonylmethoxyethyl)adenine
AUTHOR(S): Naesens, Lieve; Balzarini, Jan; Bischofberger, Norbert; De Clercq, Erik
CORPORATE SOURCE: Rega Inst. Medical Research, Katholieke Univ. Leuven, Louvain, Belg.
SOURCE: Antimicrobial Agents and Chemotherapy (1996), 40(1), 22-8
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lipophilic ester prodrugs of 9-(2-phosphonylmethoxyethyl)adenine (PMEA), i.e., bis(pivaloyloxymethyl)PMEA [bis(POM)-PMEA] and diphenyl-PMEA, have been synthesized to increase the oral bioavailability of this broad-spectrum antiviral agent. The antiretroviral efficacy was determined in severe combined immune deficiency (SCID) mice infected with Moloney murine sarcoma virus (MSV). They were treated twice daily for 5 days after infection. Oral treatment with bis(POM)-PMEA at a dose equivalent to 100 or 50 mg of PMEA per kg of body weight per day proved markedly effective in delaying MSV-induced tumor formation and death of the mice. Oral bis(POM)-PMEA afforded anti-MSV efficacy equal to that of s.c. PMEA given at equimolar doses. Oral treatment with PMEA or diphenyl-PMEA proved less efficient. Similarly, in mice infected with Friend leukemia virus (FLV), oral treatment with bis(POM)-PMEA at a dose equivalent to 100 or 50 mg of PMEA per kg per day effected a marked inhibition of FLV-induced splenomegaly (87 and 48% inhibition, resp.), the efficacy being equal to that of PMEA given s.c. at equivalent doses. Pharmacokinetic expts. with mice showed that the oral bioavailabilities of PMEA following oral gavage of bis(POM)-PMEA, diphenyl-PMEA, or PMEA (at a dose equivalent to 50 mg of PMEA per kg) were 53, 3, and 16%, resp. These data were calculated from the levels of free PMEA in plasma. Also, the recoveries of free PMEA in the urine upon oral administration of bis(POM)-PMEA, diphenyl-PMEA, or PMEA (at a dose equivalent to 25 mg of PMEA per kg) were 48, 4, and 7%, resp. Oral bis(POM)-PMEA was not recovered from plasma, suggesting that it was readily cleaved to free PMEA. In contrast, diphenyl-PMEA was not

efficiently cleaved to free PMEA, resulting in a rather low oral bioavailability of PMEA from this prodrug. Bis(POM)-PMEA appears to be an efficient oral prodrug of PMEA that deserves further clin. evaluation in human immunodeficiency virus-infected individuals.

L6 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:631079 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 123:93031
ORIGINAL REFERENCE NO.: 123:16417a,16420a
TITLE: In vivo antiretroviral efficacy of oral bis(POM)-PMEA, the bis(pivaloyloxymethyl)prodrug of 9-(2-phosphonylmethoxyethyl)adenine (PMEA)
AUTHOR(S): Naesens, L.; Neyts, J.; Balzarini, J.; Bischofberger, N.; De Clercq, E.
CORPORATE SOURCE: Rega Inst. for Medical Research, Katholieke Univ. Leuven, Louvain, B-3000, Belg.
SOURCE: Nucleosides & Nucleotides (1995), 14(3-5), 767-70
CODEN: NUNUD5; ISSN: 0732-8311
PUBLISHER: Dekker
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The bis-pivaloyloxymethyl(POM)- and diphenyl-ester prodrugs of the broad spectrum antiviral agent 9-(2-phosphonylmethoxyethyl)adenine (PMEA) have been evaluated in vivo for antiviral efficacy upon oral administration in severe combined immune deficiency (SCID) mice infected with Moloney murine sarcoma virus (MSV). Oral bis(POM)-PMEA proved highly efficient in delaying MSV-induced tumor formation and associated death, its effect being equal to that of s.c. PMEA at an equimolar dose. Compared to bis(POM)-PMEA, oral diphenyl-PMEA had lower antiviral efficacy, whereas PMEA as such was poorly effective when administered orally. The authors studies indicate that bis(POM)-PMEA must have a favorable oral bioavailability and justify its clin. investigation as an oral prodrug of PMEA in the treatment of HIV infections.

L6 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1992:625687 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 117:225687
ORIGINAL REFERENCE NO.: 117:38749a,38752a
TITLE: Pharmacokinetics in mice of the anti-retrovirus agent 9-(2-phosphonylmethoxyethyl)adenine
AUTHOR(S): Naesens, Lieve; Balzarini, Jan; De Clercq, Erik
CORPORATE SOURCE: Rega Inst. Med. Res., Kathol. Univ. Leuven, Louvain, B-3000, Belg.
SOURCE: Drug Metabolism and Disposition (1992), 20(5), 747-52
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pharmacokinetics of 9-(2-phosphonylmethoxyethyl)adenine (PMEA), a potent inhibitor of retrovirus (i.e. human immunodeficiency virus) replication was determined in mice. Upon i.v. bolus administration of PMEA at 25, 100, or 500 mg/kg, PMEA was rapidly cleared from the plasma in a monoexponential and dose-independent manner (half-life, 7-12.5 min; distribution volume, 0.30-0.36 L/kg; total body clearance, 1.21-2.41 L/h/kg). Irresp. of the initial PMEA dose, 67% of unchanged PMEA was recovered from the urine of mice within 24 h after administration of PMEA. [3H]PMEA, administered as an i.v. bolus injection, mainly accumulated in the kidney, liver, and lungs. Significant amts. of monophosphorylated PMEA were detected in

kidney and liver, but not other tissues, at 10, 30, and 60 min after i.v. administration of PMEA. Low but significant levels of PMEA were attained in the brain.

```
=> s 147127-20-6 and (lymph#### or liver or hematologic## or kidney or nephr#####
or or hepatic)
   REGistRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

L8         860 L7

MISSING TERM 'OR OR'
COMMAND STACK INTERRUPTED.  ENTER "DISPLAY HISTORY"
TO SEE WHICH COMMANDS WERE EXECUTED.

The search profile that was entered contains a logical
operator followed immediately by another operator.

=> s L8 and (hiv or immunodeficiency or hbv or hepatitis)
         81787 HIV
           108 HIVS
         81808 HIV
                 (HIV OR HIVS)
         83097 IMMUNODEFICIENCY
           848 IMMUNODEFICIENCIES
         83397 IMMUNODEFICIENCY
                 (IMMUNODEFICIENCY OR IMMUNODEFICIENCIES)
         13192 HBV
            83 HBVS
         13211 HBV
                 (HBV OR HBVS)
         70822 HEPATITIS
             1 HEPATITISES
         70822 HEPATITIS
                 (HEPATITIS OR HEPATITISES)
L9         721 L8 AND (HIV OR IMMUNODEFICIENCY OR HBV OR HEPATITIS)

=> s L9 and (administ##### or measur### or determin### or quantif#####)
        291157 ADMINIST#####
       2141839 MEASUR###
        206482 DETERMIN###
        745940 DET
         47599 DETS
        789559 DET
                 (DET OR DETS)
       2236687 DETD
        371230 DETG
       1609736 DETN
        136960 DETNS
       1690562 DETN
                 (DETN OR DETNS)
       4395243 DETERMIN###
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                (DETERMIN### OR DET OR DETD OR DETG OR DETN)
       125920 QUANTIF#####
L10       222 L9 AND (ADMINIST##### OR MEASUR### OR DETERMIN### OR QUANTIF####
                #)

=> s L10 and (pharmacokinetic# or bioavailab##### or distribution)
       110327 PHARMACOKINETIC#
        70286 BIOAVAILAB#####
      1194690 DISTRIBUTION
       221574 DISTRIBUTIONS
      1318385 DISTRIBUTION
                (DISTRIBUTION OR DISTRIBUTIONS)
L11        42 L10 AND (PHARMACOKINETIC# OR BIOAVAILAB##### OR DISTRIBUTION)

=> s L11 and py<2004
     24012934 PY<2004
L12        10 L11 AND PY<2004

=> d L12 ibib abs 1-10

L12  ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2003:754518  CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER:         139:301170
TITLE:                   Effect of tenofovir on didanosine absorption in
                         patients with HIV
AUTHOR(S):               Fulco, Patricia Pecora; Kirian, Margaret A.
CORPORATE SOURCE:        Internal Medicine, Department of Pharmacy Services,
                         Medical College of Virginia Hospitals and Physicians,
                         Virginia Commonwealth University Health System,
                         Richmond, VA, USA
SOURCE:                  Annals of Pharmacotherapy (2003), 37(9),
                         1325-1328
                         CODEN: APHRER; ISSN: 1060-0280
PUBLISHER:               Harvey Whitney Books Co.
DOCUMENT TYPE:           Journal; General Review
LANGUAGE:                English
AB   A review.  OBJECTIVE: To evaluate the pharmacokinetic
     interaction between tenofovir and didanosine when used in combination as a
     highly active antiretroviral therapy regimen.  DATA SOURCES: Literature
     retrieval was accessed through MEDLINE (1966-Jan. 2003) using the terms
     tenofovir and didanosine.  Abstrs. from recent meetings, including the
     International AIDS Society, Interscience Conference on Antimicrobial
     Agents and Chemotherapy, and the Infectious Diseases Society of America,
     were reviewed for relevant abstrs. and poster presentations.  DATA
     SYNTHESIS: Pharmacokinetic studies evaluating the concurrent use
     of tenofovir and didanosine have been performed in healthy volunteers.
     Tenofovir 300 mg administered concurrently with 400 mg
     didanosine results in a 48-64% increase in the didanosine maximum plasma
     concentration and AUC with no significant alterations in the tenofovir
     pharmacokinetic parameters.  Tenofovir 300 mg and didanosine 250
     mg has been compared with didanosine 400 mg alone.  The results
     demonstrated equivalent didanosine AUCs.  CONCLUSIONS: When used concurrently,
     tenofovir significantly increases the maximum plasma concentration and the AUC
of
     didanosine.  Addnl. data in HIV-infected patients are needed to
     determine the long-term toxicities of this combination therapy.
     Didanosine dose reduction should be considered when these 2 agents are used
     concurrently.
REFERENCE COUNT:         21    THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L12 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:595196 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 139:332254
TITLE: Sensitive determination of tenofovir in human plasma samples using reversed-phase liquid chromatography
AUTHOR(S): Sentenac, S.; Fernandez, C.; Thuillier, A.; Lechat, P.; Aymard, G.
CORPORATE SOURCE: Clinical Pharmacology and Drug Monitoring Unit, Pitie-Salpetriere Hospital, Paris, Fr.
SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2003), 793(2), 317-324
CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new HPLC assay was developed for the determination of tenofovir, a nucleotide analog, in plasma. A solid-liquid extraction procedure was coupled with a reversed-phase HPLC system. The system requires a mobile phase containing Na2HPO4 buffer, Bu4N H sulfate and MeCN for different elution through a C18 column with UV detection. The method proved to be accurate, precise and linear between 10 and 4000 ng/mL. The method was applied to determine trough levels of tenofovir in 11 HIV-infected patients with virol. failure under multiple antiretroviral therapy. This method was also successfully applied to a pharmacokinetic study in an HIV infected patient with renal failure.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:508083 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 139:374273
TITLE: Metabolism of tenofovir and didanosine in quiescent or stimulated human peripheral blood mononuclear cells
AUTHOR(S): Robbins, Brian L.; Wilcox, Carrie K.; Fridland, Arnold; Rodman, John H.
CORPORATE SOURCE: St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Pharmacotherapy (2003), 23(6), 695-701
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB As tenofovir disoproxil fumarate substantially increases plasma concns. of didanosine in patients with human immunodeficiency virus-1 infection, we sought to determine whether tenofovir and didanosine showed a similar intracellular interaction in human peripheral blood mononuclear cells (PBMCs). Comparative in vitro incubation of two antiretrovirals in lymphocytes. Clin. research laboratory Radiolabeled tenofovir and didanosine in human PBMCs. Phosphorylation of 2 and 20 μM didanosine to dideoxyadenosine triphosphate (ddATP) was detd . in quiescent and stimulated PBMCs in the presence or absence of 5 μM tenofovir. Similarly, phosphorylation of 5 μM tenofovir to tenofovir diphosphate (TFVpp) was examined in the presence or absence of 2 and 20 μM didanosine. Intracellular amts. of ddATP and TFVpp were determined by incubating PBMCs with radiolabeled tenofovir or didanosine alone and together for up to 16 h and then separating the anabolites by high-performance liquid chromatog. for quantitation. The presence of tenofovir did not affect the amount of ddATP in quiescent or stimulated PBMCs with 2 or 20 μM didanosine. In addition, didanosine did not alter the amount of TFVpp that formed. The amount of ddATP was modestly

(1.5-3-fold) but consistently higher in stimulated than in quiescent PBMCs, but the amount of TFVpp did not differ. There is no significant interaction between tenofovir and didanosine in human PBMCs as determined by the extent of formation of the phosphorylated anabolites. This suggests that adjusting didanosine dosage, when given with tenofovir, to achieve similar didanosine plasma concns., may be sufficient to accommodate the systemic drug interaction.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:427801 CAPLUS <<LOGINID::20081202>>

DOCUMENT NUMBER: 139:285557

TITLE: Liquid chromatographic assay for the antiviral nucleotide analogue Tenofovir in plasma using derivatization with chloroacetaldehyde

AUTHOR(S): Sparidans, Rolf W.; Crommentuyn, Kristel M. L.; Schellens, Jan H. M.; Beijnen, Jos H.

CORPORATE SOURCE: Department of Biomedical Analysis, Faculty of Pharmaceutical Sciences, Division of Drug Toxicology, Utrecht University, Utrecht, 3584 CA, Neth.

SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2003), 791(1-2), 227-233
CODEN: JCBAAI; ISSN: 1570-0232

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A sensitive and selective reversed-phase liquid chromatog. assay for Tenofovir in human plasma has been developed and validated. Tenofovir was isolated from a 200-μL plasma sample using protein precipitation with trichloroacetic acid. The fluorescent 1,N6-etheno derivative is formed at 98° in the buffered extract with chloroacetaldehyde. This derivative was analyzed using gradient ion-pair liquid chromatog. and fluorescence detection at 254 nm for excitation and 425 nm for emission. In the evaluated concentration range (20-1000 ng/mL), the intraday precision was 4% and the interday precision was 5-6%. An accuracy of between 97 and 110% was determined The lower limit of quantification was 20 ng/mL with an interday precision of 11%, an intraday precision of 12%, and an accuracy of 103%. The assay is subject to interference from co-administered Abacavir. The usefulness of the assay was demonstrated for samples obtained from an HIV-infected patient treated with Tenofovir.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:291152 CAPLUS <<LOGINID::20081202>>

DOCUMENT NUMBER: 138:336285

TITLE: Resting CD4+ T lymphocytes but not thymocytes provide a latent viral reservoir in a simian immunodeficiency virus-Macaca nemestrina model of human immunodeficiency virus type 1-infected patients on highly active antiretroviral therapy

AUTHOR(S): Shen, Anding; Zink, M. Christine; Mankowski, Joseph L.; Chadwick, Karen; Margolick, Joseph B.; Carruth, Lucy M.; Li, Ming; Clements, Janice E.; Siliciano, Robert F.

CORPORATE SOURCE: Department of Medicine, Johns Hopkins University

School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Journal of Virology (2003), 77(8), 4938-4949
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Despite suppression of viremia in patients on highly active antiretroviral therapy (HAART), human immunodeficiency virus type 1 persists in a latent reservoir in the resting memory CD4+ T lymphocytes and possibly in other reservoirs. To better understand the mechanisms of viral persistence, the authors established a simian immunodeficiency virus (SIV)-macaque model to mimic the clin. situation of patients on suppressive HAART and developed assays to detect latently infected cells in the SIV-macaque system. In this model, treatment of SIV-infected pig-tailed macaques (Macaca nemestrina) with the combination of 9-R-(2-phosphonomethoxypropyl)adenine (PMPA; tenofovir) and beta-2',3'-dideoxy-3'-thia-5-fluorocytidine (FTC) suppressed the levels of plasma virus to below the limit of detection (100 copies of viral RNA per mL). In treated animals, levels of viremia remained close to or below the limit of detection for up to 6 mo except for an isolated "blip" of detectable viremia in each animal. Latent virus was measured in blood, spleen, lymph nodes, and thymus by several different methods. Replication-competent virus was recovered after activation of a 99.5% pure population of resting CD4+ T lymphocytes from a lymph node of a treated animal. Integrated SIV DNA was detected in resting CD4+ T cells from spleen, peripheral blood, and various lymph nodes including those draining the gut, the head, and the limbs. In contrast to the wide distribution of latently infected cells in peripheral lymphoid tissues, neither replication-competent virus nor integrated SIV DNA was detected in thymocytes, suggesting that thymocytes are not a major reservoir for virus in pig-tailed macaques. The results provide the first evidence for a latent viral reservoir for SIV in macaques and the most extensive survey of the distribution of latently infected cells in the host.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:840904 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 139:346
TITLE: Inhibition of murine AIDS by a heterodinucleotide of azidothymidine and 9-(R)-2-(phosphonomethoxypropyl)adenine
AUTHOR(S): Rossi, Luigia; Serafini, Sonja; Franchetti, Palmarisa; Casabianca, Anna; Orlandi, Chiara; Schiavano, Giuditta Fiorella; Carnevali, Andrea; Magnani, Mauro
CORPORATE SOURCE: Institute of Biochemistry 'G. Fornaini', University of Urbino, Urbino (PU), 2-61029, Italy
SOURCE: Journal of Antimicrobial Chemotherapy (2002), 50(5), 639-647
CODEN: JACHDX; ISSN: 0305-7453
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tenofovir [9-(R)-2-(phosphonomethoxypropyl)adenine (PMPA)] and zidovudine [azidothymidine (AZT)] are potent anti-HIV agents that have shown a strong synergy in in vitro studies. In this paper we have investigated both the potentiality of this synergy in vivo and the possibility to administer AZT and PMPA simultaneously as a single drug AZTpPMPA. The pharmacokinetic studies reported here have shown that AZTpPMPA administered i.p. in mice performs as a

prodrug, providing a slow delivery of AZT and PMPA in circulation. C57BL/6 mice infected with the retroviral complex LP-BM5 were used to evaluate the efficacy of AZTpPMPA in inhibiting disease progression. Furthermore, the effectiveness of the heterodinucleotide was compared with that of AZT and PMPA, administered as single drugs, or as a combination (AZT plus PMPA). The results obtained showed that AZTpPMPA is able to reduce lymphoadenopathy (88%), splenomegaly (64%), lymph node BM5 proviral DNA content (49%) and hypergammaglobulinemia (40%). However, upon AZT plus PMPA administration, similar (splenomegaly and lymphoadenopathy reduction) or better results (64% hypergammaglobulinemia reduction and 75% lymph node BM5 proviral DNA content inhibition) were obtained. Furthermore, these results overlapped those obtained upon PMPA administration. Thus, no synergy between PMPA and AZT was observed in murine AIDS and administration of AZT does not improve the antiviral results obtained by PMPA administration.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:695941 CAPLUS <<LOGINID::20081202>>

DOCUMENT NUMBER: 137:232453

TITLE: Preparation of substituted benzophenones as inhibitors of reverse transcriptase

INVENTOR(S): Chan, Joseph Howing

PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA

SOURCE: PCT Int. Appl., 163 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002070470	A2	20020912	WO 2002-US6037	20020228 <--
WO 2002070470	A3	20030306		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2439820	A1	20020912	CA 2002-2439820	20020228 <--
AU 2002254056	A1	20020919	AU 2002-254056	20020228 <--
AU 2002254056	B2	20050929		
EP 1363877	A2	20031126	EP 2002-723265	20020228 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
HU 2003003326	A2	20040128	HU 2003-3326	20020228
BR 2002007752	A	20040323	BR 2002-7752	20020228
CN 1494528	A	20040505	CN 2002-805882	20020228
NZ 527864	A	20040528	NZ 2002-527864	20020228
JP 2004525914	T	20040826	JP 2002-569791	20020228
IN 2003KN01052	A	20050708	IN 2003-KN1052	20030819
ZA 2003006549	A	20041122	ZA 2003-6549	20030821
NO 2003003857	A	20031027	NO 2003-3857	20030901 <--
MX 2003PA07883	A	20031204	MX 2003-PA7883	20030902 <--
US 20040122064	A1	20040624	US 2004-469104	20040205

US 6995283	B2	20060207		
US 20060009651	A1	20060112	US 2005-223634	20050909
PRIORITY APPLN. INFO.:			US 2001-272953P	P 20010302
			WO 2002-US6037	W 20020228
			US 2004-469104	A3 20040205
OTHER SOURCE(S):	MARPAT 137:232453			

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1 = ≥1 substituent chosen from halo, CF3, alkyl, aminoalkyl, alkoxy, CN, NO2, NH2, thioalkoxy, etc.; R2 = H, halo, alkyl, NO2, NH2, alkylamino, CF3, alkoxy; R3 = OH, halo, CF3, NO2, alkyl; R4 = sulfonamido, sulfonylimino, etc.;] were prepared For instance, 3,5-dichlorobromobenzene was metalated (MTBE, n-BuLi, -50°) and acylated with the N,2-dimethoxy-N-methyl-5-chlorobenzamide and the resulting benzophenone converted to II. II was converted to III in 5 steps. Polymorphic forms of sodium, choline, calcium, magnesium, ethanolamine and triethylamine salts of III were prepared and characterized. Oral bioavailability and solubility parameters were determined for III and polymorphic salt forms thereof. Compds. of the present invention have anti-HIV activity and deliver compds. that have anti- HIV activity in the range IC50 = 1-1000 nM against wild type and mutant viruses.

L12 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2002:240063 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER:	136:395376
TITLE:	Phenotypic susceptibilities to tenofovir in a large panel of clinically derived human immunodeficiency virus type 1 isolates
AUTHOR(S):	Harrigan, P. R.; Miller, M. D.; McKenna, P.; Brumme, Z. L.; Larder, B. A.
CORPORATE SOURCE:	BC Centre for Excellence in HIV/AIDS, St. Paul's Hospital, Vancouver, BC, Can.
SOURCE:	Antimicrobial Agents and Chemotherapy (2002), 46(4), 1067-1072 CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER:	American Society for Microbiology
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Tenofovir is a nucleotide analog human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) inhibitor, and its oral prodrug, tenofovir disoproxil fumarate, has recently been approved for the treatment of HIV-1 infection in the United States. The objective of this study was to characterize the in vitro susceptibility profiles of a large panel of clin. derived HIV-1 isolates for tenofovir. The distribution of tenofovir susceptibilities in over 1,000 antiretroviral-naive, HIV-1-infected individuals worldwide was determined using the Virco Antivirogram assay. In addition, phenotypic susceptibilities to tenofovir and other RT inhibitors were determined in a panel of nearly 5,000 recombinant HIV -1 clin. isolates from predominantly treatment-experienced patients analyzed as a part of routine drug resistance testing. Greater than 97.5% of isolates from treatment-naive patients had tenofovir susceptibilities <3-fold above those of the wild-type controls by the Antivirogram. The clin. derived panel of 5,000 samples exhibited a broad range of antiretroviral drug susceptibilities, including 69, 43, and 16% having

>10-fold-decreased susceptibilities to at least one, two, and three antiretroviral drug classes, resp. Greater than 88% of these 5,000 clin. isolates were within the three-fold susceptibility range for tenofovir, and >99% exhibited <10-fold-reduced susceptibilities to tenofovir. Decreased susceptibility to tenofovir was not directly associated with resistance to other RT inhibitors; r2 values of log-log linear regression plots of susceptibility to tenofovir vs. susceptibility to other RT inhibitors were <0.4. The results suggest that the majority of treatment-naive and treatment-experienced individuals harbor HIV that remains within the normal range of tenofovir susceptibilities and may be susceptible to tenofovir disoproxil fumarate therapy.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:601942 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 129:310454
ORIGINAL REFERENCE NO.: 129:63189a,63192a
TITLE: Safety, pharmacokinetics, and antiretroviral activity of intravenous 9-[2-(R)-(phosphonomethoxy)propyl]adenine, a novel anti-human immunodeficiency virus (HIV) therapy, in HIV-infected adults
AUTHOR(S): Deeks, Steven G.; Barditch-Crovo, Patricia; Lietman, Paul S.; Hwang, Frances; Cundy, Kenneth C.; Rooney, James F.; Hellmann, Nicholas S.; Safrin, Sharon; Kahn, James O.
CORPORATE SOURCE: University of California, San Francisco, San Francisco, CA, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1998), 42(9), 2380-2384
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 9-[2-(R)-(Phosphonomethoxy)propyl]adenine (PMPA) is a nucleotide analog with potent antiretroviral activity in vitro and in simian models. A randomized, double-blind, placebo-controlled, dose-escalation clin. trial of i.v. PMPA monotherapy was conducted in HIV-infected adults with CD4 cell counts of ≥200 cells/mm3 and plasma HIV RNA levels of ≥10,000 copies/mL. Two dose levels were evaluated (1 and 3 mg/kg/day). On day 1, a single dose of PMPA or placebo was administered by i.v. infusion. Beginning on day 8, PMPA or placebo was administered once daily for an addnl. 7 consecutive days. All the subjects tolerated the treatment without significant adverse events. Mean peak serum PMPA concns. were 2.7 and 9.1 μg/mL in the 1- and 3-mg/kg cohorts, resp. Serum concns. declined in a biexponential fashion, with a terminal half-life of 4-8 h. At 3 mg/kg/day, a single infusion of PMPA resulted in a 0.4 log10 median decline in plasma HIV RNA by day 8. Following 7 consecutive days of drug administration thereafter, the median changes in plasma HIV RNA from basal values were -1.1, -0.6, and 0.1 log10 in the 3-mg/kg/day, 1-mg/kg/day, and placebo dose groups, resp. Following the final dose in the 3-mg/kg/day cohort, the reduction in HIV RNA was sustained for 7 days before returning toward initial values.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:189777 CAPLUS <<LOGINID::20081202>>
DOCUMENT NUMBER: 128:303590

ORIGINAL REFERENCE NO.: 128:59993a
TITLE: Pharmacokinetics and bioavailability of the anti-human immunodeficiency virus nucleotide analog 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) in dogs
AUTHOR(S): Cundy, Kenneth C.; Sueoka, Cathy; Lynch, Geoffrey R.; Griffin, Linda; Lee, William A.; Shaw, Jeng-Pyng
CORPORATE SOURCE: Gilead Sciences, Inc., Foster City, CA, 94404, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1998), 42(3), 687-690
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pharmacokinetics, bioavailability, and metabolism of the anti-human immunodeficiency virus nucleotide analog 9[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) were determined in beagle dogs following i.v., i.p., and oral administration. Fasted male beagle dogs (n = 5) were pretreated with pentagastrin and received PMPA (10 mg/kg of body weight) by the i.v. and oral routes with a washout period of 1 wk between doses. A further group of male dogs received PMPA as a single dose via the i.v. (1 mg/kg; n = 5) and the i.p. (10 mg/kg; n = 3) routes, with 1-wk washout period between doses. The concns. of PMPA in plasma and urine were determined over 48 h postdosing by fluorescence derivatization and high-performance liquid chromatog. (HPLC). The potential for metabolism or biliary excretion of PMPA was evaluated in a dog with a chronic indwelling bile cannula. Urine, feces, and bile were collected at intervals over 48 h following the i.v. administration of [14C]PMPA (10 mg/kg; 55 μCi/kg). The concns. of PMPA in plasma after i.v. injection were best described by an open two-compartment model with a terminal half-life of approx. 10 h. PMPA was excreted unchanged in urine (70%); recovery in feces (0.42%) or bile (0.26%) was negligible. The plasma clearance of PMPA (0.28 ± 0.05 L/h/kg) was substantially greater than the glomerular filtration rate in this species, suggesting active tubular secretion of PMPA. No metabolites of [14C]PMPA were observed in urine, feces, or bile on the basis of HPLC with radioactive flow detection. The remainder of the dose was probably excreted unchanged in urine beyond 48 h postdosing. The mean ± standard deviation observed bioavailabilities of PMPA following oral and i.p. administration at 10 mg/kg were 17.1% ± 1.88% and 73.5% ± 10.5%, resp.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> logoff